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BRIEF REPORT

Concurrent Chemo-Radiotherapy Potentiates Vascular Inflammation

Increased FDG Uptake in Head and Neck Cancer Patients

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Concurrent chemo-radiotherapy (CCRT) is the cornerstone of treatment for patients with head and neck cancer. However, the potential risk for cardiovascular complications after combined radiotherapy (RT) and chemotherapy is usually neglected. RT targeting the neck region has been correlated with intimal thickening and stenosis of the carotid arteries, which has been shown to increase the risk for stroke (1). In addition, chemotherapy, particularly platinum-based regimens, has been associated with increased long-term cardiovascular events (2). Despite the evidence linking the potential detrimental effects of RT or chemotherapy to vascular damage, the exact mechanism remains largely unclear. Furthermore, most previous studies have focused mainly on the intermediate-term or long-term effects of RT or chemotherapy on cardiovascular events. The acute or short-term impact of RT or chemotherapy on vascular inflammation is currently unknown.

Recently, it has been shown that ^{18}F-fluorodeoxyglucose (FDG) can be taken up by macrophages in inflammatory vascular plaque (3). Thus, vascular FDG uptake may be an important surrogate marker for vascular inflammation (4). We hypothesized that combined RT and chemotherapy causes localized and systemic vascular inflammation, which ultimately leads to atherosclerosis formation and increased risk for cardiovascular morbidities. By using serial positron emission tomographic (PET)/computed tomography (CT) hybrid scans before and during CCRT for 1 month in patients with head and neck cancer, we sought to determine whether there was increased FDG uptake over bilateral carotid arteries or other vascular walls as a result of the treatment and to explore the potential mechanisms of CCRT-related cardiovascular complications.

Seventeen consecutive patients with stage III to IVA pharyngeal cancer who underwent definitive cisplatin-based CCRT from 2009 to 2010 were enrolled in this retrospective study (certificate number of local institutional review board: DMR99-IRB-067). All of them underwent pre-treatment and interim PET/CT imaging, scheduled during the fourth week of CCRT, with the cumulative RT dose ranging from 36 to 45 Gy. All patients received concurrent chemotherapy consisting of cisplatin (80 to 100 mg/m^2 on days 1, 22, and 43). Imaging was performed with a PET/CT scanner (Discovery STE; GE Healthcare, Milwaukee, Wisconsin), and scanning began 60 min after intravenous injection of 370 MBq FDG. After determining the axial imaging range, a spiral non-contrast-enhanced low–radiation dose CT scan was performed for anatomical reference and attenuation correction. PET emission images were then acquired serially after CT scans at 2 min per field of view in 3-dimensional acquisition mode with a 1-slice overlap at the borders of the field of view.

Vendor-provided software (Xeleris, GE Healthcare) was used for processing and analysis of the PET/CT images. Vascular inflammation was assessed visually on the transaxial, coronal, and sagittal planes and was defined as increased FDG radioactivity along the vascular wall compared with the corresponding anatomical features on the CT component of PET/CT imaging. A spherical volume of interest with a diameter of 5 mm generated by the vendor-provided software was used for measuring the maximum standardized uptake value (SUV_{max}) of the vascular wall. Background blood-

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pool activity was calculated by averaging the representative SUV_{max} of the superior and inferior vena cavae. Then, the target-to-background ratio (TBR), which represents corrected vascular to background blood-pool radioactivity (5) was calculated by dividing the representative SUV_{max} of analyzed vascular segment with the background blood-pool radioactivity.

Demographic data showed that our study subjects were essentially low–cardiovascular risk patients before CCRT (Online Table 1). FDG uptake values, reported as SUV_{max} and TBR, before and 1 month after CCRT are shown in Table 1. Compared with the data before CCRT, significantly increased TBR values 1 month after CCRT were noted in the right ($p = 0.001$) and left ($p = 0.002$) carotid arteries (Fig. 1). Furthermore, the increased arterial FDG uptake was not confined to the bilateral carotid arteries. Vessels other than the carotid arteries also showed significantly increased TBR values after CCRT (Online Fig. 1), including the ascending aorta ($p < 0.001$), aortic arch ($p = 0.006$), upper thoracic descending aorta ($p = 0.001$), midthoracic descending aorta ($p = 0.001$), lower thoracic descending aorta ($p = 0.001$), and abdominal aorta ($p < 0.001$). Even at more remote sites from the irradiation target, such as the right and left iliac arteries, the TBR values also significantly increased after CCRT ($p = 0.004$ and $p = 0.002$, respectively). The SUV_{max} values after CCRT also showed a similar incremental pattern over multiple vascular segments (Table 1).

Using PET/CT imaging to evaluate vascular FDG uptakes before and after CCRT, we observed a general increase in vascular FDG uptake after treatment. Our findings suggest that cisplatin-based CCRT can trigger systemic vascular inflammation in a short period of time, which may ultimately progress to vascular atherosclerotic formation later in life. To the best of our knowledge, this is the first study using serial PET/CT scans as a tool to evaluate the short-term effects of CCRT on vascular inflammation.

Although we have undertaken a pilot study using serial PET/CT scans as a novel tool to detect CCRT-induced vascular inflammation, there were several limitations to this study. First, it was a single-center, retrospective study with a small sample size; the results need to be confirmed in large-scale studies. Second, although we identified acute vascular inflammation during CCRT, the chronic effect is still unclear in this patient population. Finally, because both RT and chemotherapy may contribute to the vascular inflammation in this study, the RT-specific or cisplatin-specific effects on the post-treatment vascular FDG uptake change remain to be elucidated. We believe that further large-scale prospective studies with long-term follow-up are necessary to clarify these questions.

In conclusion, serial PET/CT examinations show increased systemic vascular FDG uptake after cisplatin-based CCRT in patients with head and neck cancer. These preliminary results suggest that the increased atherothrombotic event rate seen after CCRT may be related to vascular inflammation induced by CCRT, and PET/CT imaging could be used to identify effective treatment options that may reduce and/or prevent CCRT-induced vascular inflammation in these patients.

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Table 1. Vascular FDG Uptake on PET/CT Imaging Before and During CCRT

Location	SUV_{max}			TBR		
	Before CCRT	During CCRT	p Value	Before CCRT	During CCRT	p Value
Right carotid artery	1.424	1.563	0.037	0.7 ± 0.1	0.9 ± 0.2	0.001
Left carotid artery	1.477	1.601	0.029	0.8 ± 0.1	1.0 ± 0.2	0.002
Ascending aorta	2.018	2.260	0.006	1.1 ± 0.1	1.3 ± 0.3	<0.001
Aortic arch	2.061	2.152	0.298	1.1 ± 0.2	1.3 ± 0.4	0.006
Upper thoracic descending aorta	1.903	2.130	0.009	1.0 ± 0.1	1.2 ± 0.2	0.001
Midthoracic descending aorta	1.856	2.035	0.097	1.0 ± 0.2	1.2 ± 0.3	0.001
Lower thoracic descending aorta	1.871	2.021	0.031	1.0 ± 0.2	1.2 ± 0.3	0.001
Abdominal aorta	1.871	2.022	0.033	1.0 ± 0.2	1.2 ± 0.3	<0.001
Right iliac artery	1.499	1.612	0.256	0.8 ± 0.1	0.9 ± 0.2	0.004
Left iliac artery	1.582	1.693	0.124	0.8 ± 0.1	1.0 ± 0.1	0.002

TBR values are mean ± SD. The Wilcoxon signed-rank test was used to determine the statistical differences of FDG uptake values between serial PET/CT examinations before and during CCRT.
CCRT = concurrent chemo-radiotherapy; CT = computed tomography; FDG = ^{18}F-fluorodeoxyglucose; PET = positron emission tomography; SUV_{max} = maximal standardized uptake value; TBR = target-to-background ratio.

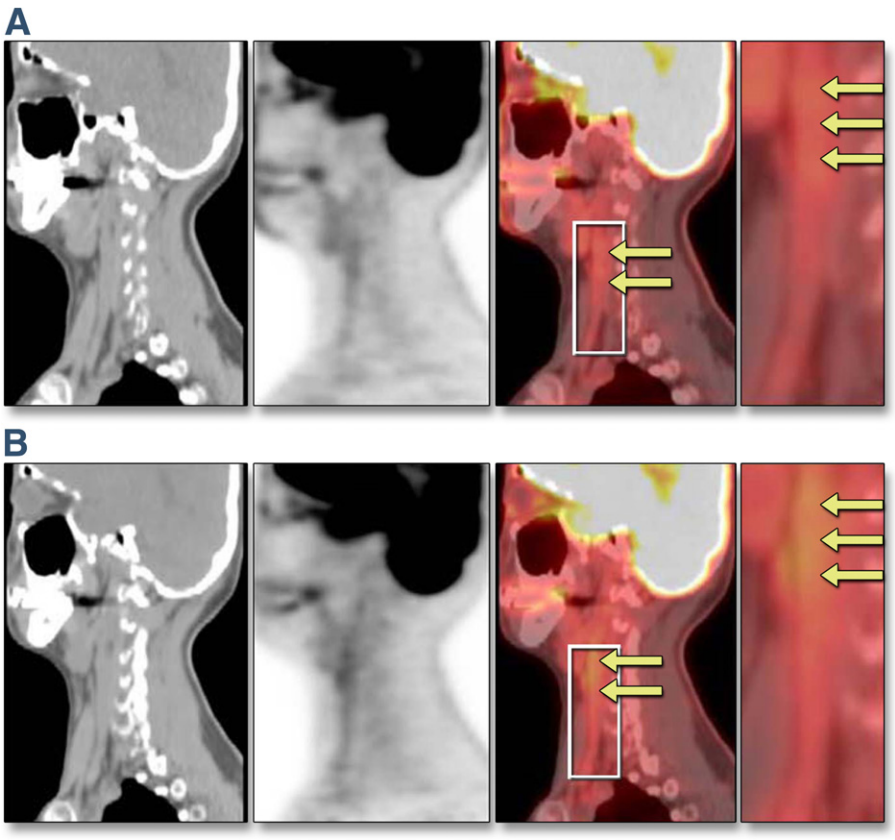

Figure 1. Sagittal Imaging of the Left Carotid Artery Before and During Cisplatin-Based CCRT

Images from left to right: coregistered computed tomography (CT), ^{18}F-fluorodeoxyglucose (FDG) positron emission tomographic (PET), fused PET/CT, and focally magnified images of the left carotid artery (frames) from PET/CT fusion scan. **(A)** Indicates images before CCRT and **(B)** represents images during CCRT. **Arrows** indicate areas of inhomogenously increased vascular FDG uptake after concurrent chemo-radiotherapy (CCRT).

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Key Words: CCRT ■ head and neck cancer ■ PET/CT hybrid imaging ■ vascular inflammation.

▶APPENDIX

For a supplementary table and figure and their legends, please see the online version of this article.